Pilot Study to Estimate the Healthcare Cost Associated with Clinical Events in Vascular Ehlers-Danlos Syndrome

Authors

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BACKGROUND

Ehlers-Danlos syndromes (EDS) are a heterogeneous group of connective tissue disorders, the most serious subtype of which is the vascular Ehlers-Danlos syndrome (vEDS).

- EDS includes many clinical subtypes with widely different phenotypes and prognoses.
- vEDS is the most serious subtype of EDS, caused by mutations in the *COL3A1* gene, resulting in defective type III collagen protein.
- Defective type III collagen in the walls of arteries and hollow organs leads to tissue fragility and increased susceptibility to rupture.
- vEDS has an unpredictable course that may lead to premature death from spontaneous arterial or organ ruptures.
- The median age of death for vEDS patients is 51 years[1].
- There is significant unmet medical need for improving outcomes in patients with vEDS.

Despite the severity of vEDS relative to other subtypes of EDS, United States medical coding groups all EDS under a single code. This has limited studying vEDS outcomes and standard of care.

- Majority of vEDS patients are diagnosed following a major complication (70%) at an average age of 28 years[1].
- The current standard of care in the U.S. is behavioral modification to reduce potential mechanical sheer stress on vessels[2].
- While there are no approved medications to treat vEDS, some physicians reportedly treat patients with antihypertensives, but how often these are used and whether there is any effect on the rate of clinical events in vEDS are not well studied.
- In addition to the high morbidity and mortality associated with vEDS clinical events, there is also an expected high healthcare cost associated with treatment and interventions for these serious clinical events, including costs related to surgery and hospital care.

To distinguish vEDS patients from other subtypes of EDS, we developed an inception cohort strategy to identify patients with rupture events using real-world evidence from a large administrative claims database (Figure 1).

- The International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10) as well as the Current Procedural Terminology (CPT) were reviewed to identify diagnosis and procedure codes pertinent to vEDS.
- vEDS is clinically suspected in patients with any of the major diagnostic criteria[3]: (1) family history of vEDS; (2) arterial rupture; (3) spontaneous sigmoid colon perforation; (4) uterine rupture during pregnancy; or (5) carotid-cavernous sinus fistula formation.
- We selected diagnosis, laboratory test, and procedure codes that indicate one of the above major diagnostic criteria.

OBJECTIVE

We utilized insurance claims patterns to differentiate vEDS patients from other subtypes of EDS and used this information to estimate clinical event rates and healthcare resource utilization associated with these events.

METHODS

Data: This study used data from Truven MarketScan®, an administrative database covering over 190 million patients across the United States, of which ~90 million were actively enrolled during the study period (2014-2017). The database includes medical, laboratory, drug prescription, and procedure claims. Use of medical services is recorded in the database with date of service, provider-type, associated diagnoses, and performed procedures. This database is compliant with the Health Insurance Portability and Accountability Act. Because the data are commercially available and deidentified, institutional review board approval was not required.

Study design: Administrative claims data, including diagnosis, procedure, and laboratory tests, were evaluated over a four-year identification period from January 1, 2014 to December 31, 2017. Patients were identified as having EDS if they had at least 2 medical claims for an EDS diagnoses on different days, separated by at least 2 months; requiring 2 separate EDS diagnoses helped to minimize misdiagnoses. Patients with suspected vEDS were further identified using the inclusion criteria described below. Because hypermobility is common in many subtypes of EDS, but uncommon in vEDS, patients with claims for hypermobility syndrome were excluded.

Inclusion criteria for suspected vEDS: Patients were suspected of having vEDS if they met all of the following criteria in their administrative claims history:

- ≥2 claims for a diagnosis of EDS (ICD-9: 756.83, ICD-10: Q79.6) separated by ≥2 months.
- ≥1 code of diagnosis, laboratory test, or procedure indicating presence of one vEDS major criteria for diagnosis (**Table 1**).
- No claims for hypermobility syndrome (ICD-9: 728.5, ICD-10: 728.5).

Rate of clinical events: To determine the rate of rupture events in the suspected vEDS patient population, we evaluated claims related to organ rupture or related clinical events over the same four-year period. We limited evaluation to a subgroup of suspected vEDS patients with ≥1 year of claims history preceding the first EDS diagnosis. By ensuring at least 1 year of prior claims history, we could confirm that each claim for a clinical event indicated the initial claim for the event and did not reflect claims for follow up encounters for remote clinical events. Claims were grouped into one of five different categories of clinical events, based on literature reports of the most common events in vEDS populations (**Table 2**). Total patient counts for each clinical event category were reported. Counts were limited to one clinical event per category (e.g., arterial rupture, intestinal perforation, etc.) for each patient per year to prevent duplicate counting for follow up encounters. Patients with one or more clinical event meeting the above criteria were categorized as have 1, 2, 3, or ≥4 clinical events over the study period.

Comparison of clinical event rates with or without antihypertensive therapy: To determine the potential effect of antihypertensive therapy on vEDS clinical event rates, we searched claims data of our vEDS population for national drug code (NDC) claims. Patients were defined as being on antihypertensive therapy if they had three or more NDC claims over the four-year study period. All other patients were defined as being on no antihypertensive therapy. Classes of antihypertensive drugs included in this analysis were beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers. We then compared the rate of clinical events between vEDS patients on each class, any, and no antihypertensive therapies. Statistical analyses were carried out with two proportion *Z*-tests. *P*-values <0.05 were considered statistically significant. All statistical tests were two-sided.

Calculation of clinical event related cost: Healthcare costs were calculated for clinical events that occurred in the first three years of the study period (2014-2016). Clinical events that occurred in the final year of the study (2017) were excluded from the cost analysis because adequate follow up claims would not be available to fully account for costs. To determine the total healthcare cost associated with each clinical event, we summed the total cost of all claims dated after the clinical event, if the claim (1) also included the original event diagnosis claim and (2) was submitted within a time interval deemed reasonable by a consensus of physician experts. This cost time interval was estimated for each type of clinical event as depicted in **Table 2**. Total cost included the sum of payments made by both patient and insurance provider. Patient lost income or disability-adjusted life year calculations were not included in cost analysis.

Figure 1. Study Design and Inclusion Criteria for Suspected vEDS Patients

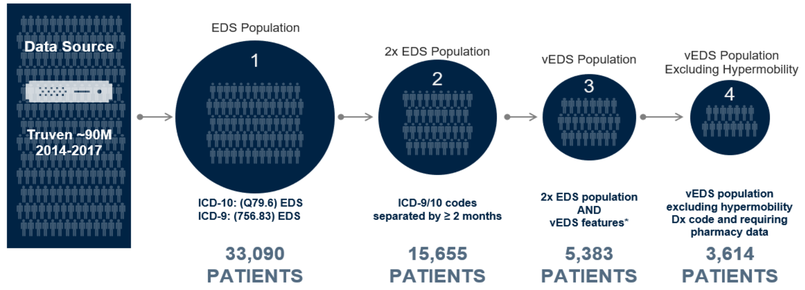


Table 1. Claims Used to Identify vEDS Patients

Claim Type	Diagnosis, Test, or Procedure
Diagnosis Codes	Aneurysm and/or dissection:
	Carotid artery
	Cerebral artery
	Iliac artery
	Splenic artery
	Thoracic aorta
	Vertebral artery
	Carotid-cavernous fistula
	Hemorrhagic stroke (age <40 y)
	Intestinal rupture
	Uterine rupture
Laboratory Tests	*COL3A1* genetic testing
Procedure Codes	Surgical or endovascular repair:
	Carotid artery
	Carotid-cavernous fistula
	Iliac artery
	Splenic artery
	Thoracic aorta
	Vertebral artery
	Angiography
	Blood transfusion

Table 2. Claims Used to Identify Clinical Events

Event Category	Excluded Diagnoses	Included Diagnoses	Cost Interval Following Event (Days)
Aneurysm	Abdominal aorta	Large- or medium-sized arteries	30
Arterial rupture	Abdominal aorta	Rupture/dissection of arteries	120
	Coronary arteries	Heart wall aneurysm/rupture	120
		Carotid-cavernous sinus fistula	90
Intestinal perforation	Gastrointestinal hemorrhage	Bowel wall rupture	150
	Perforated ulcers		
Intracranial hemorrhage	Ischemic stroke	Intraparenchymal hemorrhage	90
	Embolic stroke	Stroke (age <45 years)	90
		Subarachnoid hemorrhage	90
		Subdural hemorrhage	45
Pneumothorax	Pulmonary hemorrhage	Pneumothorax	30

Table 3. Patient Characteristics

	No. (%)	
Variable	**Sample Size**	**vEDS Patients**
Total patients	89,078,064	3,614
Male	42,288,940 (47.5%)	749 (20.7%)
Female	46,789,124 (52.5%)	2,865 (79.3%)
Age category (y)		
<18	22,976,388 (25.8%)	582 (16.1%)
18-34	23,903,365 (26.8%)	1,301 (36.0%)
35-44	11,915,550 (13.4%)	716 (19.8%)
45-54	12,073,794 (13.6%)	508 (14.1%)
55-64	11,803,168 (13.3%)	369 (10.2%)
≥65	6,405,799 (7.2%)	138 (3.8%)

Figure 2. Patients with Multiple Events

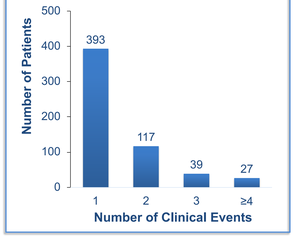


Figure 3. Rate of Clinical Events

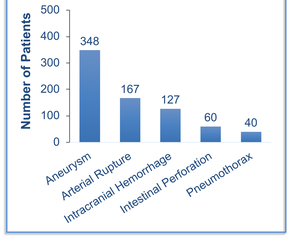


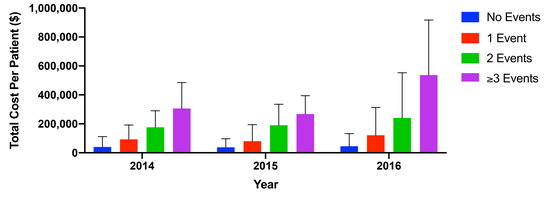
Table 4. Rate of Clinical Events in vEDS Patients on Antihypertensive Therapy

vEDS Patient Group	No. Patients (%)	Rate of Clinical Events	*P*-value (vs. No Antihypertensive)
No antihypertension therapy	2,371 (65.6%)	371 (15.6%)	-
Any antihypertension therapy	1,243 (34.4%)	205 (16.5%)	0.51
Beta blocker	895 (24.8%)	146 (16.3%)	0.64
ACE inhibitor	231 (6.4%)	38 (16.5%)	0.75
Angiotensin receptor blocker	228 (6.3%)	55 (24.1%)	0.999
Calcium channel blocker	254 (7.0%)	33 (13.0%)	0.27

Table 5. Cost of Clinical Events

	Cost Per Clinical Event		
Clinical Event	**Mean**	**Median**	**Standard Deviation**
Aneurysm	$14,909	$3,062	$44,768
Arterial Rupture	$82,131	$13,762	$196,104
Intestinal Perforation	$161,323	$38,679	$414,823
Intracranial Hemorrhage	$75,089	$13,594	$190,332
Pneumothorax	$70,725	$39,390	$108,195

Figure 4. Total Healthcare Cost Per Patient Per Year (Mean with SD)



RESULTS

Demographic and antihypertensive usage analysis: Summarized in **Table 3**. The base sample population consisted of 89,078,064 million patients with roughly equal numbers of males and females. There were 3,614 suspected cases of vEDS. Compared to the base sample population, vEDS patients were younger with a mean age of 35 years and 36% of the patients between the ages of 18 and 34 years. There were more female cases in both the EDS and vEDS patient populations. The vEDS population was 79% female and 21% male.

Rate of clinical events: 15.9% of vEDS patients had ≥1 clinical event, and of those patients 31.8% had multiple events, with an overall average rate of 1.19 events per year (**Figure 2**). Of the total 745 events, 348 (46.7%) involved arterial aneurysm, 167 (22.4%) arterial rupture, 127 (17.0%) intracranial hemorrhage, 60 (8.1%) intestinal perforation, and 40 (5.4%) pneumothorax (**Figure 3**).

Effect of antihypertensive usage of rate of clinical events: Of the 3,614 vEDS patients identified, 2,371 (65.6%) were on no antihypertensive therapy and 1,243 (34.4%) were on antihypertensive therapy. The number of vEDS patients on each medication and the rate of clinical events for each group is shown in **Table 4**. There was no statistically significant difference between rate of clinical events in patients in any of the medication groups compared to patients on no antihypertensive medication.

Cost of clinical events: Data are summarized in **Table 5** and **Figure 4**. We found a wide range of costs per documented clinical event, even within the same category of events. However, on average, costs ranged from ~$15K to ~$160K per event with aneurysms costing the least and intestinal perforations costing the most. Over the entire 3,614 suspected vEDS patients identified in this study, the cost per patient per year increased substantially between patients without clinical events and those who had at least one clinical event. The costs increased proportionally for patients with 2, 3, and ≥4 clinical events.

LIMITATIONS

- Reliance on administrative claims data to diagnose vEDS, without confirmatory biochemical or genetic testing, limits the certainty of vEDS diagnosis in our study population.
- Medical codes lack the granularity to capture unique characteristics of a rare disease such as vEDS, lowering the sensitivity and specificity of our approach.
- Although we employed a broad range of ICD and CPT codes to capture clinical events, it is possible that capture was sub-optimal and not all clinical events were captured accurately.
- The True database sample population may have different demographic characteristics than the United States population as a whole, limiting generalizability of our approach.

CONCLUSIONS

- This study assessed the clinical burden and healthcare costs associated with clinical events in patients with vEDS in the United States.
- Using big data claims analyses and vEDS-associated clinical event criteria, we identified a presumed vEDS population based on phenotypic presentation.
- The prevalence of vEDS in our population is slightly higher than expected based on reported prevalence for genotypically-confirmed cases of *COL3A1* mutation carriers. Therefore, we may be capturing some additional phenotypically similar subtypes of EDS or those due to mutations other than *COL3A1*.
- Demographics of our population were similar to prior reports.
- The rate of clinical events, including arterial ruptures and intestinal perforations, reflects a high clinical burden for these patients.
- Patients on antihypertensive therapy, regardless of agent class, had no significant reduction in clinical event rates compared to patients on no antihypertensive therapy.
- High healthcare costs are accrued for follow up care and interventions in response to vEDS events, and costs increase proportionally to the number of events endured by each patient.
- Our results suggest that current antihypertensive therapies are not effective at reducing the high risks of serious clinical events in vEDS patients.
- It is imperative that comprehensive efforts are geared towards approval of an effective treatment to reduce the high clinical burden and healthcare costs associated with vEDS.

REFERENCES

1. Pepin MG, *et al.* Genet Med, 16, 881-888, (2014)
2. Adam MP, *et al.* "Vascular Ehlers-Danlos Syndrome-GeneReviews." (1993-2018)
3. Malfait F, *et al.* Am J Med Genet C Semin Med Genet, 175, 8-26, (2017)

DISCLOSURES

BK and TF are employed by HVH Precision Analytics, which received funding for this research from Acer Therapeutics Inc. ST is a former employee and WA is a current employee of Acer Therapeutics Inc.